Author's response to reviews

Title: Evaluation of an early step-down strategy from IV anidulafungin to oral azole therapy for the treatment of candidemia and other forms of invasive candidiasis: results from an open-label trial

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Author's response to reviews: see over
Dear Dr Harris

RE: Evaluation of an Early Step-Down Strategy from Intravenous Anidulafungin to Oral Azole Therapy for the Treatment of Candidemia and Other Forms of Invasive Candidiasis: Results from an Open-label Trial

Following your letter of July 1, 2013, we have compiled a response to the journal editor and the peer reviewers, and have revised the manuscript accordingly. My co-authors and I would be very grateful if you would again consider this manuscript for publication in BMC Infectious Diseases.

We look forward to hearing from you.

Yours faithfully

Robert Swanson, PhD
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<td><strong>Editor</strong></td>
<td><strong>Thank you for your comments.</strong></td>
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<td>1. The topic is important with potential implications for future guidelines and the paper is well written overall. However, the reviewers have raised important issues that the authors should address in their revision. The most important limitation of this study as noted by the authors is that it &quot;was not appropriately designed for statistical comparison between the early switch subpopulation and the MITT.&quot; The authors should clarify what hypotheses or questions the study was in fact designed to answer. The major comparison in this study is between the MITT population and the early switch population. While the outcomes in the early switch group were comparable to the MITT group, I suspect that this population was less sick than the group that did not switch early. Although a direct comparison between the early and non-early switch groups would not be appropriate for assessing efficacy, the authors should consider a comparison to highlight potential characteristics that may identify patients amenable to an early switch.</td>
<td>The authors would like to emphasize that this was not a hypothesis-generating study. The general aims of the study were to collect data on the efficacy, safety and tolerability of anidulafungin, for at least five days, followed by oral azole therapy with either fluconazole or voriconazole in patients with invasive candidiasis or candidemia. <strong>Background, Page 6, lines 89-92.</strong> The following text has been inserted: ‘The study was specifically designed to evaluate anidulafungin treatment in a broad group of patients with C/IC caused by various species of Candida and to explore use of an early step-down strategy in a real world setting.’ <strong>Methods, Page 10, line 182-184.</strong> The following text has been inserted: ‘No formal hypotheses were tested in this study and the design did not allow for statistical comparisons to be made between the early switch subpopulation and the MITT population.’ Unfortunately, we cannot directly compare the early switch subpopulation and the MITT population because early switch subpopulation was contained within the ITT population. Instead we have tried to qualitatively indicate some of the differences in baseline characteristics between the early switch subpopulation and the MITT population. <strong>Discussion, Pages 14-15, lines 253-263.</strong> The following text has been inserted: ‘Although baseline characteristics for the early switch subpopulation were generally similar to the overall MITT population, some interesting differences were noted. In the early switch subpopulation compared with the overall MITT population, C. glabrata isolates were less common. Importantly, fewer early switch patients had an APACHE-II score &gt;20 and fewer had a length of</td>
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ICU stay ≥4 days. This suggests that patients in the early switch subpopulation were less severely ill. In general, the early switch subpopulation showed response rates similar to the MITT population and these response rates were maintained through the end of study. These results demonstrate the efficacy of including an early step-down strategy in treating patients with C/IC.

| 2. Would suggest changing "regimes" to "regimens" throughout. | The manuscript has been revised accordingly. |
| 3. The introduction could be shortened with emphasis that current IDSA guidelines regarding switch to oral therapy is not based on prospective studies. | **Background, Pages 4-5, lines 62-76.** The text has been revised as follows:  

> ‘In vitro, the echinocandins (including anidulafungin) have reported potent fungicidal activity against most *Candida* species and demonstrated a favorable safety profile [12-18]. Echinocandins are recommended as the treatment of choice for severely ill and neutropenic patients with proven or suspected invasive candidiasis in recent clinical practice guidelines [13]. An azole, such as fluconazole, is widely used and recommended as a first-line agent for the treatment of C/IC in non-critically ill patients [13]. Voriconazole is also recommended as a step-down therapy for patients with infection due to some of the NAC species following first-line treatment with an echinocandin or amphotericin B.’

**Background, Page 5, lines 78-86.** The text has been revised as follows:  

> ‘The Infectious Diseases Society of America (IDSA) guidelines include the recommendation to step-down to oral azole therapy as early as possible once the patient is clinically stable and blood cultures have become negative [13]. The European Society for Clinical Microbiology and Infectious Diseases (ESCMID) suggests simplification of treatment by stepping down to oral fluconazole after 10 days of treatment if the patient is stable, and tolerates oral therapy, and if the *Candida* species is susceptible [19]. However, neither of these specific strategies has been prospectively studied and the appropriate timing of step-down therapy remains unclear.’

| 4. Was antifungal prophylaxis an exclusion criteria? | Prior antifungal prophylaxis was not one of the exclusion criteria and was permitted as long as it was discontinued prior to the study and no signs and symptoms of candidemia were present. |
| **5. If removal of catheters was "required" within 24 hours, why was the definition of catheter removal "by study Day 3?"** | **Methods, Page 7, lines 109-112.** The text has been revised as follows:  
‘Patients were allowed to participate if they had received no more than 48 hours of systemic azole therapy. Prior prophylaxis with azoles was permitted provided it was discontinued prior to the study.’ |
|---|---|
| **5. If removal of catheters was "required" within 24 hours, why was the definition of catheter removal "by study Day 3?"** | **Methods, Page 7, lines 120-122.** The text has been revised as follows:  
‘To allow for delays in scheduling catheter removal in these seriously ill patients, patients who had all catheters removed or replaced to another anatomical location by study Day 3 were considered to have had their catheters removed.’ |
| **6. Would specify in the Tables if any of the differences were statistically significant.** For example, ICU stay and C. glabrata were more common in the MITT group than in the early switch group. | **Thank you for your comment. Unfortunately, we cannot directly compare early switch and MITT populations because early switch is contained within the ITT population. Instead we have tried to qualitatively indicate some of the differences in baseline characteristics between the early switch subpopulation and the MITT population.** |
| **Discussion, Pages 14-15, lines 253-263.** The following text has been inserted:  
‘Although baseline characteristics for the early switch subpopulation were generally similar to the overall MITT population, some interesting differences were noted. In the early switch subpopulation compared with the overall MITT population, C. glabrata isolates were less common. Importantly, fewer early switch patients had an APACHE-II score >20 and fewer had a length of ICU stay ≥4 days. This suggests that patients in the early switch subpopulation were less severely ill. In general, the early switch subpopulation showed response rates similar to the MITT population and these response rates were maintained through the end of study. These results demonstrate the efficacy of including an early step-down strategy in treating patients with C/IC.’ | **7. The duration of IV was a median of 6 days in the MITT and 5 days in the early switch. A comparison of early switch vs. non-early switch would be helpful in confirming that there was a significant difference in duration of IV which would be essential to understanding the relevance of this data.** |
| **7. The duration of IV was a median of 6 days in the MITT and 5 days in the early switch. A comparison of early switch vs. non-early switch would be helpful in confirming that there was a significant difference in duration of IV which would be essential to understanding the relevance of this data.** | **Thank you for your comment. Table 2 has been revised to include data from the late switch subpopulation and the no switch subpopulation.** |
| **Results, Pages 11-12, lines 203-207.** The following text has been inserted:  
‘There were 48 patients in the late switch subpopulation; the median duration of IV therapy prior to oral step-down was 10.0 days (range, 4–27)** |
and the median duration of overall antifungal therapy was 19.0 days (range, 8–42). The durations of therapy for the MITT population, and the early switch subpopulation, late switch subpopulation, and no switch subpopulation are shown in Table 2.’

**Reviewer 1**

1. This is a well-written paper; however, there are a number of limitations due to the design of this study. The major limitation of this study is the inability to make comparisons directly between different groups of patients. This has been noted by the authors.

   Thank you for your comments.

2. The authors report extensively on two populations only, the MITT population of 250 patients and the early switchers comprised of 102 patients. In reality, there appears to be two other groups: 48 late switchers and 100 non-switchers. Where these populations different? Also, some mortality data is reported; however, the authors might consider presenting length of survival curves separately for the populations of interest.

   Thank you for your comment. Table 2 has been revised to include data from the late switch subpopulation and the no switch subpopulation.

   **Results, Pages 11-12, lines 203-207.** The following text has been inserted:

   ‘There were 48 patients in the late switch subpopulation; the median duration of IV therapy prior to oral step-down was 10.0 days (range, 4–27) and the median duration of overall antifungal therapy was 19.0 days (range, 8–42). The durations of therapy for the MITT population, and the early switch subpopulation, late switch subpopulation, and no switch subpopulation are shown in Table 2.’

   Survival curves have not been included in the manuscript as the authors do not believe that they provide any additional information.

3. Overall, the real conclusion for this paper should state for those patients that were switched by their physicians to early oralazole therapy, there appeared to be no significant issues regarding such switch. In addition, the authors should better detail how patients were selected to be an early switcher or not as a limitation of the study.

   **Methods, Page 8, lines 128-130.** The following text has been inserted:

   ‘Patients were not randomized or pre-selected to receive early oral step down therapy; rather the decision was made based on the patient’s condition and protocol guidelines.’

   **Discussion, Pages 14-15, lines 253-263.** The following text has been inserted:

   ‘Although baseline characteristics for the early switch subpopulation were generally similar to the overall MITT population, some interesting differences were noted. In the early switch subpopulation compared with the overall MITT population, *C. glabrata* isolates were less common. Importantly, fewer early switch patients had an
APACHE-II score >20 and fewer had a length of ICU stay \( \geq \) 4 days. This suggests that patients in the early switch subpopulation were less severely ill. In general, the early switch subpopulation showed response rates similar to the MITT population and these response rates were maintained through the end of study. These results demonstrate the efficacy of including an early step-down strategy in treating patients with C/IC.

4. Specifically, the conclusion that patients could safely receive oral therapy should be caveated better. Namely, these patients had been selected to switch and were likely less ill than those who did not switch or not likely to have GI issues affecting oral absorption.

Discussion, Pages 14-15, lines 253-263. The following text has been inserted:

‘Although baseline characteristics for the early switch subpopulation were generally similar to the overall MITT population, some interesting differences were noted. In the early switch subpopulation compared with the overall MITT population, *C. glabrata* isolates were less common. Importantly, fewer early switch patients had an APACHE-II score >20 and fewer had a length of ICU stay \( \geq \) 4 days. This suggests that patients in the early switch subpopulation were less severely ill. In general, the early switch subpopulation showed response rates similar to the MITT population and these response rates were maintained through the end of study. These results demonstrate the efficacy of including an early step-down strategy in treating patients with C/IC.’

**Reviewer 2**

1. Methods, study treatment: Were susceptibilities of *Candida* isolates verified? As the authors imply in the discussion, the high response rates noted are likely reflective of antifungal activity. However, I believe that provision of antifungal susceptibility data would be an important addition to the paper and likely of interest to readers. Also, was fluconazole dosing adjusted in patients with reduced creatinine clearance as it appears that patients with renal insufficiency were not excluded?

Susceptibilities were confirmed for all Candida isolates obtained from this study. To keep the manuscript to a limited length, we decided to report on susceptibility data as part of a subsequent manuscript which also pools microbiology data from other studies.

2. Methods, study assessments, safety: I believe that there needs to be more details provided regarding safety/adverse event monitoring, perhaps in a newly created table, to further support the claim of safety of step-down azole therapy in this study. Specifically what parameters were proactively monitored? For example, were routine safety assessments made during IV

Thank you for your comment; however, to keep the manuscript within the word limits imposed by the journal, the requested information was not included.

**Methods, Page 10, lines 173-174.** The following text has been inserted:

‘Routine safety assessments were made during IV
baseline and serial QTc intervals (especially given the 20 and 25% rates of hypokalemia in the MITT and early switch arms, respectively, as noted in table 1) and LFTs examined in patients on azoles? Was concomitant receipt of other medications with the potential for QTc prolongation evaluated in patients stepped down to azoles (see AAC. 2013;57(3):1121-7)? Were drug interactions screened for in patients on azoles?

| 3. | Table 1: The ANC term used in the table needs to be clarified (i.e. is ANC intended to be \(>10^3/mm^3\))? It should also be clarified how there are 2 patients with ANC \(<500\) in the early switch arm, when these patients were stated as exclusions in the Methods. There are also 2 categories of “No” in the catheter removal section of this table that need to be clarified. | Thank you for your comment. Table 1 refers to patients with neutropenia at baseline. Such patients were allowed to switch to oral therapy if their neutropenia resolved before the switch occurred. There were several cases in which the patient’s condition (eg. severe thrombocytopenia, etc) prevented the removal of a suspected catheter. |
| 4. | Methods, study treatment: It is stated that treatment was given for at least 14 days after the last positive blood/tissue culture. The authors should clarify if this is indeed the case, or if the duration was at least 14 days after the first negative culture. Because blood cultures were obtained every day, the difference between these 2 durations is likely to not differ by much, but should still be clarified for consistency. | The authors confirm that treatment was given for at least 14 days after the last positive blood/tissue culture. |
| 5. | Background, 4th paragraph: The fact that the ESCMID candidemia guidelines only marginally recommend fluconazole with a level C rating, while moderately recommending voriconazole with a level B rating could also be addressed. | Introduction, Page 5, lines 82-86. The following text has been inserted: The European Society for Clinical Microbiology and Infectious Diseases (ESCMID) suggests simplification of treatment by stepping down to oral fluconazole after 10 days of treatment if the patient is stable, and tolerates oral therapy, and if the Candida species is susceptible [19]. However neither of these specific strategies have been prospectively studied and the appropriate timing of step-down therapy remains unclear. |
| 6. | Background, 5th paragraph: The ESCMID candidemia guidelines endorse azole step-down therapy after 10 days of initial IV therapy and not “as early as possible” as with the IDSA guidelines. Again, I think | Introduction, Page 5, lines 82-86. The following text has been inserted: The European Society for Clinical Microbiology and Infectious Diseases (ESCMID) suggests |
| there is an opportunity to expand the discussion to include both sets of guidelines. | simplification of treatment by stepping down to oral fluconazole after 10 days of treatment if the patient is stable, and tolerates oral therapy, and if the *Candida* species is susceptible [19]. However neither of these specific strategies have been prospectively studied and the appropriate timing of step-down therapy remains unclear. |